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Original Article

Insulin Resistance and Other Comorbidities of Obesity as Independent Variables on Ventricular Repolarization in Children and Adolescents

Zehra Ilhan[1], Mervan Bekdas[1*], Mehmet Inanir[2], and Nimet Kabakus[1]

[1]Department of Pediatrics, Bolu Abant Izzet Baysal University Medical Faculty, Bolu, Turkey
[2]Department of Cardiology, Bolu Abant Izzet Baysal University Medical Faculty, Bolu, Turkey
ORCID:
Mervan Bekdas: https://orcid.org/0000-0003-2469-9509

Abstract

Background: Obesity, a rapidly increasing global health problem in all age groups, is accepted as the basis for many chronic diseases through insulin resistance mechanism. This study aimed to examine whether insulin resistance and other comorbidities of obesity have an effect on the cardiac conduction system.
Methods: The study included 50 obese and 47 healthy individuals aged 6–18 years. ECGs of all cases were taken; ECG waves and intervals were measured manually.
Results: Of the obese group, 19 were boys (38%) and 31 were girls (62%), 27 were children (54%) and 23 were adolescents (46%), their ages were 11.3 ± 3.5 years. These particular characteristics were similar compared to the control group. However, in the obese group, the ECG parameters QTc (p = 0.001), QTd (p < 0.001), QTdc (p < 0.001), JTc (p < 0.001), Tp-e (p < 0.001), Tp-e/QT (p < 0.001), Tp-e/QTc (p < 0.001), Tp-e/JT (p < 0.001), and Tp-e/JTc (p < 0.001) were significantly longer. Twenty-five obese subjects (50%) had insulin resistance, when ECG parameters are compared to those without it, only JTc was significantly longer (332.3 ± 16.5 vs 321.7 ± 17.7 ms, p = 0.033). JTc duration mostly affected JT (p < 0.001) and QTc (p < 0.001). The 327 ms cut-off value of JTc indicated insulin resistance in the obese patients (p = 0.044) (sensitivity 60%, specificity 60%).
Conclusion: Insulin resistance and other comorbidities of obesity may cause ventricular repolarization abnormalities at an early age. JTc, an ECG parameter, can be a guide in assessing ventricular repolarization abnormality and the risk of arrhythmia in these patients.

Keywords: obesity, insulin resistance, comorbidities, ventricular repolarization, child, adolescence

Corresponding Author: Mervan Bekdas; email: merbek14@yahoo.com

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1. Introduction

The World Health Organization defines obesity as an excessive accumulation of body fat that may have a negative effect on health [1]. Obesity is accepted as a rapidly increasing global health problem in all age groups in all developed and developing countries [2].

Over the past 40 years, the obesity rate in children and adolescents has increased by 7 times [3]. According to the 2013 data of Turkey Childhood Obesity Research Initiative Study (COSI-TUR) which assessed children aged 7–8 years, 8.3% of children were obese, (6.6% girls, 10% boys) [4]. In the COSI-TUR 2016 study, which was repeated three years later, this rate was found to be 9.9% (8.5% in girls, 11.3% in boys), these values showed an increase of 19.3% in childhood obesity (28.8% in girls and 13% in boys), even in the short-term period. These values showed that 1 out of every 10 children in our country is obese [5].

Obesity, which is one of the most common chronic manifestations of childhood, is accepted as the basis for many chronic diseases, these are complications such as hepatosteatosis, type 2 diabetes mellitus, hypertension, dyslipidemia, atherosclerosis, coronary artery disease, and cerebrovascular diseases [6, 7]. Insulin resistance creates the basis for these complications. Insulin resistance expresses the decreasing response to the normal level of circulating insulin [8].

Prolonged QT interval, a marker of ventricular repolarization, has previously been identified as a risk factor for sudden cardiac death (SCD) [9, 10], and subsequent Mendelian randomization experiments have shown that this risk factor is causal [11]. On the other hand, population-based studies have shown that early repolarization is associated with an increased risk of cardiac death in Western and Asian general populations [12–14]. SCD is seen in 6–14% patients without demonstrable structural heart disease [15]. Therefore, rapid diagnosis of early repolarization has a major importance. Haïssaguerre *et al.* [15] reported changes compatible with early repolarization in 31% of cases with fatal arrhythmias such as ventricular fibrillation, whereas Nam *et al.* [16] reported the same results for 60% of the cases. Our aim in this study is to investigate whether insulin resistance leading to different pathologies in obese causes changes in ventricular repolarization, which is an indicator of ventricular arrhythmia.

2. Materials and Methods

In this prospective study conducted between February 2018 and September 2019, obese patients between the ages of 6 and 18 years and referred to the pediatrics clinic of our hospital were included. Obesity was determined as a body mass index (BMI) above the 95-percentile and considering the age and gender of the patients. Obese people did not have any other chronic disease and history of drug use. During the same period, 47 patients who did not have a chronic disease, did not use drugs, and had a BMI between 5 and 85 percentiles were also selected to form the control group. When individuals were referred to the outpatient clinic, informed consent was obtained from them and/or parents. Patients other than 6–18 years old, smokers, those with chronic diseases, type 1 diabetes, and familial hypercholesterolemia and those who did not give consent were not included in the study.

A detailed history was taken from the participants, and physical examinations were performed. Serum insulin, which is one of the biochemical tests, was measured by the chemiluminescence method (Roche e601). Insulin resistance was calculated according to the formula of HOMA-IR (Homeostasis Model Assessment of Insulin resistance; serum fasting blood sugar × serum insulin/405) [17]. Insulin resistance was considered to be HOMA-IR value > 2.2 in girls and >2.6 in boys in the prepubertal period and >3.8 in girls and >5.2 in boys in the pubertal period [18].

For ECG shots, individuals were rested for 10 min, then ECG shots of 10 mm/mV amplitude and 25 mm/s velocity were performed with 12 channel ECG device (Nihon Kohen Cardiofax ECG-1950 VET) in a supine position. Ventricular repolarization was accepted as the interval (QT interval) from the beginning of the QRS complex to the end of the T wave [19]. Measurements such as QT and corrected QT intervals (QTc) were used to demonstrate cardiac repolarization heterogeneity and to identify patients at risk. In addition, T wave peak and endpoint interval (Tp-e) were used to show ventricular repolarization disorder in recent years [20]. Tp-e/QT and Tp-e/QTc ratios calculated based on this index are accepted as electrocardiographic indicators of ventricular arrhythmogenesis [21]. Repolarization indicators JT and JTc are accepted as a useful marker in defining the risk of arrhythmia [22]. In our cases, all these intervals were measured manually by a cardiologist using a magnifying glass (TorQ 150 mm Digital Caliper LCD).

2.1. Statistical analysis

SPSS (Statistical Package for Social Sciences) program version 21 was used for statistical evaluation. Numerical data are presented as mean ± SD and categorical data as percentile (%) numbers. Student's *t*-tests were used in the analysis of variables with normal distribution, and Mann–Whitney U-tests were used in the analysis of non-normally distributed or categorical variables. $P < 0.05$ was used as the level of significance. Univariate linear regression analysis was used to determine the variables affecting the ECG parameters, for this, variables with $p < 0.05$ were used in the correlation analysis. The receiver operating characteristic (ROC) curve was used to determine the threshold

ECG value, the area under the ROC curve, specificity and sensitivity, and cut-off points were calculated.

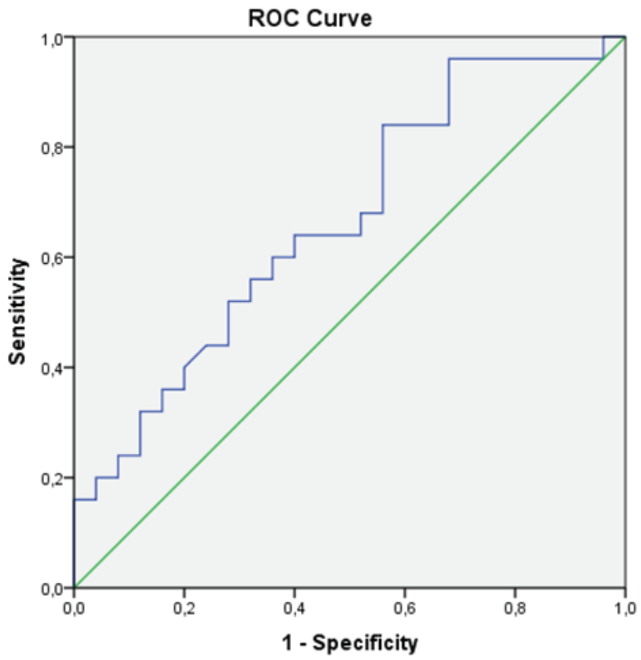

Figure 1: ROC curve analysis for JTc.

3. Results

Fifty obese and forty-seven healthy subjects between the ages of 6 and 18 years were included in the study. There was no significant difference between the two groups in terms of age, age group, and gender. Although there was a significant difference in the clinical data regarding BMI, blood pressures, fasting blood sugar, insulin, HOMA-IR, HbA1c, and lipid profile in obese group, there was no significant difference for other variables (Table 1).

Compared to the control group, a statistically significant difference was determined in ECG parameters such as QTc, QTd, QTdc, JTc, Tp-e, Tp-e/QT, Tp-e/QTc, Tp-e/JT, and Tp-e/JTc in the obese group, while the other parameters were not different (Table 2).

Twenty-five obese subjects (50%) had insulin resistance, while the control group had none. There was no significant difference between the two groups in terms of age, age group, BMI, and blood pressures, but there was a significant difference in the gender, fasting blood sugar, insulin, HOMA-IR, and triglyceride-to-HDL ratio in insulin resistance group (Table 3).

Table 1: Comparison of demographic and clinical data of the groups.

Features	Obese (n = 50)	Control (n = 47)	P-value
Age (yr)	11.3 ± 3.5	11.6 ± 2.9	0.28
Age group (C/A)(n)	27/23	23/24	0.62
Gender (M/F) (n)	19/31	23/24	0.67
BMI	28.7 ± 5.8	17.6 ± 3.2	<0.001
BMI percentile	97.6 ± 2.7	39.7 ± 28.5	<0.001
BMI z-score	2.1 ± 0.4	–0.3 ± 0.9	<0.001
Systolic BP	115 ± 14.6	101.7 ± 13.4	<0.001
Diastolic BP	75 ± 11.5	63.7 ± 9.8	<0.001
Sodium (mmol/l)	137.5 ± 2.2	138.5 ± 3.1	0.068
Potassium (mmol/l)	4.5 ± 0.2	4.4 ± 0.2	0.2
Calcium (mg/dl)	9.9 ± 0.4	9.84 ± 0.4	0.12
Magnesium (mg/dl)	1.9 ± 0.1	1.9 ± 0.1	0.3
FBS (mg/dl)	88.7 ± 10.6	84 ± 12.7	0.05
Insulin (μIU/ml)	21.3 ± 28.3	7.2 ± 3.5	0.001
HOMA-IR	5.1 ± 8.4	1.5 ± 0.8	0.005
HbA1c (%)	5.51 ± 0.29	5.3 ± 0.22	<0.001
Hgb (g/dl)	13.6 ± 1	13.4 ± 0.7	0.32
Cholesterol (mg/dl)	167.5 ± 28.6	160.6 ± 44.7	0.36
Triglycerides (mg/dl)	122.6 ± 71.4	66 ± 30.5	<0.001
LDL (mg/dl)	89.3 ± 25.2	85.3 ± 15.8	0.36
HDL (mg/dl)	51.6 ± 11.3	68.9 ± 86.9	0.16
LDL/HDL	1.81 ± 0.64	1.53 ± 0.43	0.017
Cholesterol/HDL	3.36 ± 0.81	2.84 ± 0.76	<0.001
Triglycerides/HDL	2.57 ± 1.8	1.21 ± 0.66	0.002

M: Male; F: Female; C: Child; A: Adolescent; BMI: Body mass index; BP: Blood pressure; FBS: Fasting blood sugar; HOMA-IR: Homeostasis Model Assessment of Insülin Resistance; HbA1c: Hemoglobin A1c; Hgb: Hemoglobin; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Compared to those without insulin resistance, only the JTc values were statistically significantly different in the ECGs of those with insulin resistance (332.3 ± 16.5 vs 321.7 ± 17.7 ms, p = 0.033), no significant difference was observed in terms of other values ($p > 0.05$; Table 4). Compared to those without insulin resistance, gender, lipids, and blood pressure did not affect the JTc value in the insulin resistance group ($p > 0.05$).

When we made the regression analysis, we found that JT (B = 0.31, 95% CI [0.18–0.44], $p < 0.001$) and QTc (B = 0.58, 95% CI [0.4–0.76], $p < 0.001$) affected the JTc time most ($r^2 = 0.72$, $p < 0.001$).

The cut-off value for JTc was determined as 327 ms in our study. Accordingly, patients with JTc values higher than 327 ms have insulin resistance (AUC: 0.66, 95% CI [0.51–0.81], p = 0.044) (sensitivity 60%, specificity 60%; Figure 1).

TABLE 2: Comparison of ECG parameters of obese and control groups.

Features	Obese (n = 50)	Control (n = 47)	P-value
QRS (ms)	83.0 ± 8.5	83.9 ± 10.2	0.62
QTmax (ms)	362.9 ± 25.6	361.5 ± 23.9	0.78
QTmin (ms)	339.8 ± 25.3	346.6 ± 24.2	0.11
Pulse (/minute)	88.8 ± 15.1	81.7 ± 12.9	0.016
RR (second)	0.69 ± 0.11	0.75 ± 0.11	0.023
QT (ms)	351.3 ± 25.2	354.1 ± 23.9	0.58
QTc (ms)	423.7 ± 19.5	410.5 ± 17.6	0.001
QTd (ms)	23.1 ± 7.8	14.8 ± 5.6	<0.001
QTdc (ms)	27.9 ± 8.6	17.3 ± 6.6	<0.001
JT (ms)	271.4 ± 23.8	265.3 ± 21.6	0.19
JTc (ms)	327.0 ± 17.8	307.4 ± 17.5	<0.001
Tp-e (ms)	85.7 ± 9.9	71.2 ± 6.8	<0.001
Tp-e/QT	0.24 ± 0.2	0.20 ± 0.2	<0.001
Tp-e/QTc	0.20 ± 0.02	0.17 ± 0.01	<0.001
Tp-e/JT	0.31 ± 0.4	0.27 ± 0.3	<0.001
Tp-e/JTc	0.26 ± 0.3	0.23 ± 0.02	<0.001

ms:Milliseconds; QRS: Ventricular depolarization time; QTmax: Longest time showing ventricular depolarization and repolarization; QTmin: Ventricular depolarization and repolarization, shortest time; RR: Distance between two Rs; QT: QTmax + QTmin sum; QTc: Corrected QT; QTd: Difference between QTmax and QTmin; QTdc: Corrected QT dispersion; JT: QRS end (point J) to the end of the T wave; JTc: Corrected JT; Tp-e: The time between the peak point of the T wave and the end of the T wave.

4. Discussion

In this study, which was carried out for the first time in this age group, we found that insulin resistance and other comorbidities of obesity may cause ventricular repolarization abnormalities.

Obesity causes several health problems, one of which is dyslipidemia. In our study, we found that the ratio of triglycerides to HDL was significantly higher in both obese and insulin-resistant patients. It is known that this finding obtained in our study can be used to estimate insulin resistance in nonobese patients [23].

The relationship between insulin resistance and gender is controversial. Insulin resistance is claimed more frequently in males [24]. On the other hand, we found that insulin resistance was higher in girls, and this result was attributed to the majority of our patients being girls in our study. Our conclusion was consistent with the literature [25].

It is known that childhood obesity is a major risk factor for cardiovascular disease in adulthood [26]. Over time, these patients develop hypertension, left ventricular hypertrophy, and impaired left ventricular diastolic function [27]. These are the causes that

TABLE 3: Comparison of the biochemical values of the groups according to insulin resistance.

Features	Insulin resistance (+) (n = 25)	Insulin resistance (–) (n = 25)	P-value
Age (yr)	11.6 ± 3.2	11 ± 3.7	0.52
Age group (C/A)(n)	13/12	14/11	0.62
Gender (M/F) (n)	4/21	15/10	0.002
BMI	30 ± 6.4	27.5 ± 5	0.13
BMI percentile	98 ± 1.5	97.3 ± 3	0.32
BMI z-score	2.1 ± 0.4	2.1 ± 0.3	0.84
Systolic BP	117 ± 14.7	112.9 ± 14.4	0.31
Diastolic BP	77.3 ± 12.7	72.7 ± 9.8	0.16
Sodium (mmol/l)	137 ± 2.5	138 ± 1.8	0.1
Potassium (mmol/l)	4.5 ± 0.3	4.5 ± 0.2	0.85
Calcium (mg/dl)	10 ± 0.4	9.9 ± 0.3	0.2
Magnesium (mg/dl)	1.9 ± 0.18	1.9 ± 0.1	0.63
FBS (mg/dl)	92.3 ± 11.4	85.2 ± 8.6	0.016
Insulin (μIU/ml)	32.4 ± 37	10.3 ± 4.2	0.005
HOMA-IR	8 ± 11.2	2.21 ± 0.97	0.013
HbA1c (%)	5.56 ± 0.32	5.46 ± 0.25	0.21
Hgb (g/dl)	13.7 ± 0.9	13.4 ± 1	0.24
Cholesterol (mg/dl)	173.1 ± 24.3	161.9 ± 31.8	0.17
Triglycerides (mg/dl)	159.2 ± 82.3	86.1 ± 29.6	<0.001
LDL (mg/dl)	87.1 ± 22.5	91.4 ± 27.9	0.55
HDL (mg/dl)	49.7±10.6	53.5±11.9	0.23
LDL/HDL	1.82±0.56	1.79±0.71	0.9
Cholesterol/HDL	3.58±0.72	3.14±0.85	0.053
Triglycerides/HDL	3.4±2	1.74±0.97	0.001

M: Male; F: Female; C: Child; A: Adolescent; BMI: Body mass index; BP: Blood pressure; FBS: Fasting blood sugar; HOMA-IR: Homeostasis Model Assessment of Insülin Resistance; HbA1c: Hemoglobin A1c; Hgb: Hemoglobin; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

increase mortality. In addition, sudden cardiac death can occur in obese children without significant structural abnormalities. In this case, attention was drawn to ventricular repolarization anomalies. Abnormalities in the stage of ventricular repolarization, which is a complex electrical event, are considered as an important risk factor for ventricular arrhythmias, one of the causes of sudden cardiac death [28]. For this purpose, prolonged QT and QTc have been used in ECG, especially long QTc has been shown to cause cardiac arrhythmias such as ventricular tachycardia and fibrillation [29]. Guven *et al.* [30] reported that obese patients had longer QTc periods than normal individuals. In our study, QTc times were longer in obese children and adolescents, however, we could

Table 4: Comparison of the ECG parameters of the groups according to insulin resistance.

Features	Insulin resistance (+) (n = 25)	Insulin resistance (-) (n = 25)	P-value
QRS (ms)	80.8 ± 9	85.2 ± 1.5	0.067
QTmax (ms)	357.3 ± 25.2	368.5 ± 25.3	0.12
QTmin (ms)	335.7 ± 24.4	343.9 ± 26	0.25
Pulse (/min)	92.4 ± 15.7	85.2 ± 13.9	0.091
RR (second)	0.06 ± 0.1	0.72 ± 0.12	0.082
QT (ms)	346.5 ± 24.6	356.2 ± 25.4	0.11
QTc (ms)	426.5 ± 17.4	420.9 ± 21.4	0.31
QTd (ms)	21.6 ± 6.8	24.6 ± 7	0.12
QTdc (ms)	26.6 ± 8.5	29.1 ± 8.7	0.3
JT (ms)	269.9 ± 19.9	272.8 ± 27.5	0.67
JTc (ms)	332.3 ± 16.5	321.7 ± 17.7	0.033
Tp-e (ms)	83.7 ± 10.1	87.7 ± 9.6	0.16
Tp-e/QT	0.24 ± 0.02	0.24 ± 0.03	0.55
Tp-e/QTc	0.19 ± 0.02	0.2 ± 0.02	0.1
Tp-e/JT	0.31 ± 0.04	0.32 ± 0.05	0.3
Tp-e/JTc	0.25 ± 0.03	0.27 ± 0.03	0.054

ms: Milliseconds; QRS: Ventricular depolarization time; QTmax: Longest time showing ventricular depolarization and repolarization; QTmin: Ventricular depolarization and repolarization, shortest time; RR: Distance between two Rs; QT: QTmax + QTmin sum; QTc : Corrected QT; QTd: Difference between QTmax and QTmin; QTdc: Corrected QT dispersion; JT: QRS end (point J) to the end of the T wave; JTc: Corrected JT; Tp-e: The time between the peak point of the T wave and the end of the T wave.

not find a relationship between insulin resistance and this parameter. This suggests that obesity prolongs QTc regardless of insulin resistance in children and adolescents.

There are some who are skeptical about the relationship between prolonged QTc distance and ventricular arrhythmia [31]. Therefore, it has been suggested to use different parameters in estimating the risk of arrhythmia. For this purpose, the Tp-e interval, which corresponds to the time of ventricular repolarization, has begun to be used [32]. Studies have shown that prolongation in the Tp-e interval is associated with ventricular arrhythmia [33] and SCD [34]. There are publications stating that Tp-e/QT and Tpe/QTc derived from these parameters can be used in the early prediction of ventricular arrhythmias that may develop [35], and there are also opponents [36]. Our study has shown that these parameters are affected in obese children and adolescents, as well as in adults.

Unlike QT, which shows both depolarization and repolarization, the JT interval shows only the ventricular repolarization period [37]. Inanir *et al.* [38] found that Tp-e/QT and Tp-e/QTc were also prolonged in addition to Tp-e, which is one of the new markers showing ventricular repolarization in adult morbid obese. Tp-e/JT derived from Tp-e and JT, which reflect the area of ventricular repolarization alone, is considered as a more valuable marker than Tp-e/QT in reflecting repolarization anomalies [38]. The JT interval varies depending on the heart rate, it is recommended to use the JTc, the heart rate-corrected form of this parameter, to use JT more effectively [39]. QTc and JTc are alternatives for each other because elongation in both values has been associated with increased risk of ventricular arrhythmia [40], however, JTc is considered to more accurately reflect ventricular repolarization [41]. Apart from Tp-e, JT and JTc, it is stated that the increase in Tp-e/JT and Tp-e/JTc derived from these parameters can also be used in the determination of ventricular repolarization anomaly [38]. In our study involving children and adolescent obese patients, prolonged detection of Tp-e/JT and Tp-e/JTc suggested that these parameters could be used in predicting ventricular arrhythmia at this age. Even in the absence of cardiac disease, weight-stable obese persons have a higher risk of arrhythmias and sudden death, and the risk of SCD increases with increasing weight [42].

Our study showed that JTc times were longer in children and adolescents with insulin resistance (332.3 ± 16.5 vs 321.7 ± 17.7, p = 0.033), this result showed that insulin resistance except obesity increased ventricular repolarization abnormality. Ventricular repolarization anomalies may cause ventricular tachyarrhythmias. Ventricular tachyarrhythmias leading to SCD may occur even in obese individuals without heart disease [43].

It can be said that insulin resistance in obese children and adolescents is an independent risk factor that may prolong the JTc, which is an indicator of ventricular repolarization disorder.

The limitation of our study is that it is a single-center study with a low number of individuals. Multicenter and larger series are needed for more precise results.

5. Conclusion

Insulin resistance and other comorbidities of obesity may cause ventricular repolarization abnormalities at an early age. JTc, an ECG parameter, can be a guide in assessing ventricular repolarization abnormality and the risk of arrhythmia in insulin-resistance patients.

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Ethical Considerations

The study protocol was approved by the ethics committee of Abant İzzet Baysal University (No. 2018/31).

Competing Interests

The authors declared no potential conflicts of interest.

Availability of Data and Materials

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